Comparison of pre-mixed and sequentially intrathecal administration of Clonidine with hyperbaric Bupivacaine in caesarean sections

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Abstract— *Adjuvant* and *hyperbaric Bupivacaine mixing in a single syringe before injecting the drugs intrathecally is an age old practice. It may cause intraoperative hemodynamic changes. Administering local anesthetic and the adjuvant separately may minimize these side effects. So this study was aimed to compare effect of administering hyperbaric Bupivacaine and Clonidine intrathecally as a mixture and sequentially in cases undergoing caesarean section (CS). This study conducted at a District Hospital of Rajasthan in year 2013. Cases undergoing elective caesarean sections were divided into two groups by chit box method each of two groups consists of 30 cases. One group (Group A) is given mixture of Clonidine (75 mcg) and hyperbaric Bupivacaine 0.5% (10 mg) intrathecally, whereas other Group B received Clonidine (75 mcg) followed by hyperbaric Bupivacaine 0.5% (10 mg) through separate syringes. It was found that duration of analgesia was significantly longer in Group B (466 ± 18.2 min) in which the drug was given sequentially than in Group A (334 ± 16 min). Likewise, the time to achieve highest sensory and complete motor block was significantly less in Group B than Group A. So it can be depicted that administering Clonidine and hyperbaric Bupivacaine in a sequential manner is better than mixing of the two drugs.*

Key words: Clonidine, Hyperbaric Bupivacaine, Spinal Anaesthesia, Adjuvants, Caesarean Section

1. Introduction

Spinal anesthesia has been widely used for caesarean section deliveries because of greater maternal safety, foetal benefits, higher parental satisfaction, and consumer demand.[1] However; various adjuvants are added intrathecally with spinal local anaesthetics to improve the quality of anesthesia and analgesia [2] Clonidine, is one of the commonly used opioids, is being used as a safe adjuvant to intrathecal local anesthetic & free of opioid related side effects. [3,4] and is known to increase both sensory and motor block of spinal anesthesia. [3] Studies have shown that Clonidine also has anti-hyperanalgesic effect so reduces the post‑operative analgesic requirement. [4,5,6] Mixing adjuvant with spinal anesthesia in a single syringe before injecting the drugs intrathecally is an old age practice, which may affect the density of both the drugs, hence their spread in cerebrospinal fluid as well as action.[7,8,9]

Administering spinal anesthesia and the adjuvants separately, it may have some different role than administering both as a mixture. Rational behind using two separate syringes for hyperbaric Bupivacaine & Clonidine administration is to minimize effect on density of both the drugs. Thus this study was planned to compare effect of administering hyperbaric Bupivacaine and Clonidine intrathecally as a mixture and sequentially in cases undergoing caesarean section.

2. Methodology

A single blind randomized comparative interventional study was carried out on sixty cases identified for caesarean section with singleton pregnancy. Cases having multiple pregnancies, any maternal or foetal complications, patients on cardiovascular medications and those having history of hypersensitivity to Clonidine and spinal anesthesia were excluded from the study.

These sixty cases identified for caesarean section were randomly allocated to Group A or Group B through chit box method. Each one of the two groups had 30 cases. Group A received hyperbaric Bupivacaine (0.5%) 10 mg (2 mL) and Clonidine 75 mcg (0.5 mL) as a mixture. Group B received Clonidine 75 mcg (0.5 mL) followed by hyperbaric Bupivacaine (0.5%) 10 mg (2 mL) in different syringes.

After recording of baseline parameters, heart rate (HR) and Blood pressure was monitored. After all pre-anasthetic procedures intrathecal drug was injected in L3-L4 interspace in Group A as mixure of hyperbaric Bupivacaine (0.5%) 10 mg (2 mL) and Clonidine 75 mcg (0.5 mL) and in Group B Clonidine 75 mcg (0.5 mL) followed by hyperbaric Bupivacaine (0.5%) 10 mg (2 mL) in different syringes.

When the block was performed, cases were monitored for Haemodynamic parameters such as HR, systolic arterial pressure (SAP), diastolic arterial pressure along with achievement of sensory and motor anesthesia.

Post‑operatively any incidence of bradycardia, hypotension, nausea/vomiting, prolonged sedation additional analgesic given reported by the recruited post- operative care unit staff was also recorded. Any other side effect of anesthesia was also noted if any.

Data thus collected were compiled in Microsoft Excel 2007 worksheet. Quantitative data is represented as Mean ± standard deviation and qualitative data presented as frequency (Number/%).

Significance of difference in means were inferred by unpaired 't' Test and significance of difference in proportion of adverse effects was inferred by Chi-square test. $P < 0.05$ was considered significant.

3. Results

Before going to compare the effect of both the type of anesthesia these two groups were matched in terms of age, height and weight in the present study. And both the groups were found comparable without any significant difference in mean age, height and weight. (Table 1)

Table No. 1
Matching of Mixture (A) Group and Sequential (B) Group

S. No.	Variables	Group A (Mixture) (N=30) Mean±SD	Group B (Sequential) (N=30) Mean±SD	Unpaired 't'Test P Value LS
1	**Age (years)**	24.64±4.4	25.86± 4.6	-1.050 at 58 DF 0.298 NS
2	**Weight (Kgs)**	152.6±4.8	154.4±5.2	-1.393 at 58 DF 0.169 NS
3	**Height (Cms)**	60.4±4.2	62.6±4.8	-1.889 at 58 DF 0.064 NS

This study also observed that although the onset time of sensory and motor block was significantly more ($p<0.05$) in sequential (Group B) than other group (Mixture Group A) but the time taken for highest level of sensory and motor block achieved was significantly less ($p<0.001$) in sequential (Group B) than other group (A). (Table 2)

Mean time to reach maximal sensory block height was significantly less in Group B (sequential) than in Group A (Mixture) i.e. 3.2±0.12 and 4.4±0.24 minutes respectively. And sensory regression to T10 was significantly high in Group B (sequential) than Group A (Mixture) i.e. 242.4±16.4 and 148.6±12.12 minutes respectively.

Complete motor blockade was achieved earlier in Group B (sequential) than in Group (Mixture) A (4.2±0.40 and 4.8±0.38 minutes respectively). The resolution time of motor block was significantly prolonged in Group B than in Group A (Mixture) i.e. 294.2±14.4 and 182±16.4 minutes respectively. (Table 2)

Table No. 2
Comparison of effect of Mixture (A) Group and Sequential (B) Group on Anaesthesia

S. No.	Variables	Group A (Mixture)(N=30) Mean±SD	Group B (Sequential)(N=30) Mean±SD	Unpaired 't'Test P Value LS
1	**Onset time of Sensory block (s)**	58±6.4	62±6.2	-2.459 at 58 DF 0.017 S
2	**Time to reach maximum Sensory block height (min)**	4.4±0.24	3.2±0.12	24.495 at 58 DF <0.001 S
3	**Sensory Regression time to T10 (min)**	148.6±12.12	242.4±16.4	-25.194 at 58 DF <0.001 S
4	**Onset time of Motor block (s)**	1.4±0.20	1.6±0.26	-3.340 at 58 DF 0.001 S
5	**Time to complete motor block (Bromage IV) (min)**	4.8±0.38	4.2±0.40	5.956 at 58 DF <0.001 S
6	**Resolution time of motor block (min)**	182±16.4	294.2±14.4	-28.158 at 58 DF <0.001 S

Present study also revealed that total duration of analgesia lasted significantly (p<0.001) longer in Group B i.e. in sequential group (466 ± 18.2 minutes) as compared to Group A i.e. Mixture Group (334 ± 16 minutes). (Fig. 1)

Use of analgesic and vasopressure was not found with significant variation (P>0.05) in both the groups. (Fig 2)

Figure 1

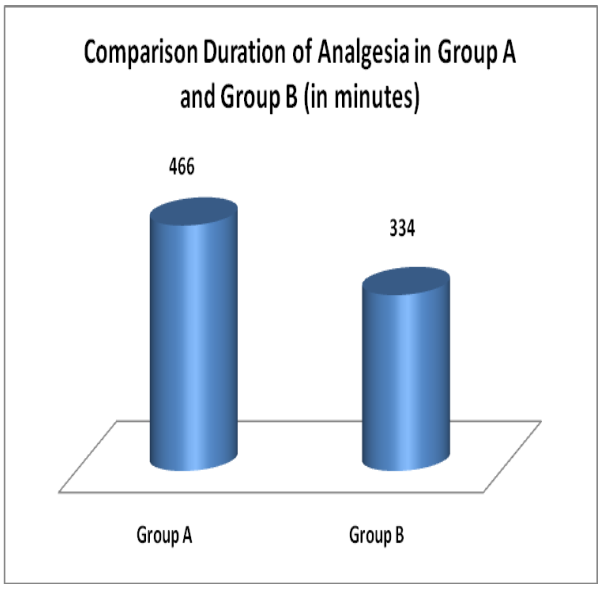
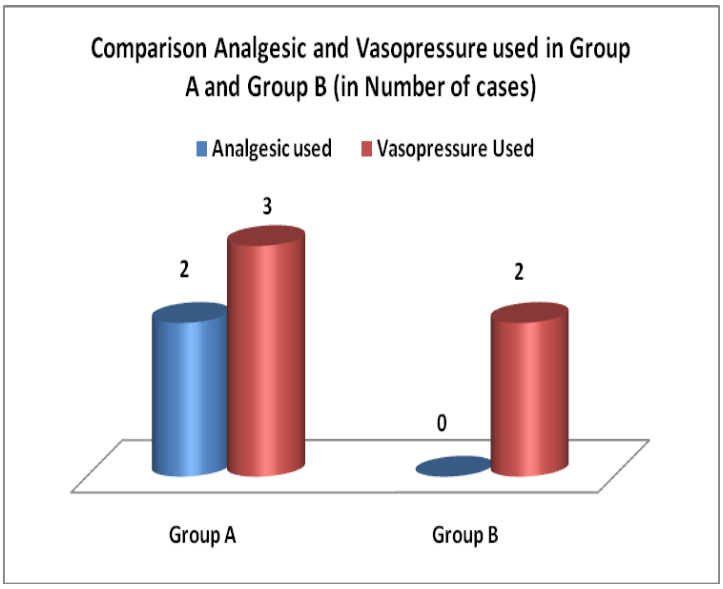


Figure 2



Duration of Analgesia: Unpaired 't' Test = 29.835 at 58 DF P<0.001 LS=S

Proportion of cases with Analgesia used: Chi-square Test = 0.517 at 1 DF P=0.472 LS=NS

Proportion of cases with Vasopressure used: Chi-square Test = 0.009 at 1 DF P=0.999 LS=NS

Like wise, Adverse side effects like Hypotension, Bradycardia, nausea and vomiting were also not found with significant variation (P>0.05) in both the groups. (Table 3)

Table No. 3
Comparison of effect of Mixture (A) Group and Sequential (B) Group on Haemodynamics

S. No.	Variables	Group A (Mixture) (N=30) Mean±SD	Group B (Sequential) (N=30) Mean±SD	Chi-square Test P Value LS
1	**Hypotension**	15	12	0.269 at 1 DF 0.604 N S
2	**Bradycardia**	2	0	0.517 at 1 DF 0.472 N S
3	**Nausea/vomitting**	5	2	0.647 at 1 DF 0.421 N S

4. Discussion:

Present study observed that sequential technique provides early onset & prolongs the duration of analgesia without significant adverse effects. Clonidine a selective partial α-2 agonist has been proven to be of benefit for intrathecal use by increasing the duration & intensity of pain relief, also by decreasing the systemic & local inflammatory stress response by other studies also.[10-13]

Various authors have used different doses of intrathecal Clonidine ranging from 15 mcg to 300 mcg along with local anesthetics. Kaabachi *et al*[14] used 2 mcg/kg of IT Clonidine and reported extended duration of post- operative analgesia whereas Sethi *et al*[6] used 70 mcg of Clonidine and found a significant decrease in mean arterial pressure and HR in Clonidine

group but no therapeutic intervention was required for either. Hence, 75 mcg of preservative free Clonidine was used in this study as an adjuvant for spinal anesthesia in CS.

As present study observed sequential technique provides early onset & prolongs the duration of analgesia without significant adverse effect. Desai *et al*[8] and Prachee S etall[15]studied the same effect by adding opioids to spinal anesthesia solution intrathecally.

It was also observed in present study that although the onset time of sensory and motor block was significantly more ($p<0.05$) in sequential (Group B) than other group (A) but the time taken for highest level of sensory and motor block achieved was significantly less ($p<0.001$) in sequential (Group B) than other group (A). Onset of sensory block does not get any better after a particular dose as supported by a study done by Heo *et al*[16] who did not report any difference in onset time even after using 150 mcg Clonidine. The time to reach maximum sensory block height and maximum motor block was significantly less in Group B (sequential drugs) than in Group A (mixed drugs) in this study. This difference might have existed because of the preferential cephalad spread of Clonidine by administering it through a separate syringe, owing to its hypobaric nature which is lost when the drugs are premixed. Desai *et al*[8] also observed that the time to reach highest level of block was less when morphine and Fentanyl were administered sequentially with spinal anesthesia than when given as a mixture.

In present study it was also found that the mean time to reach maximal sensory block height was significantly ($p<0.001$) less in Group B (sequential drugs) than in Group A (mixed drugs) . And sensory regression to T10 was significantly ($p<0.001$) high in Group B than Group A i.e. 242.4±16.4 and 148.6±12.12 minutes respectively. Complete motor blockade was achieved earlier in Group B than in Group A and the resolution time of motor block was significantly ($p<0.001$) prolonged in Group B than in Group A i.e. 294.2±14.4 and 182±16.4 minutes respectively. Present study also revealed that total duration of analgesia lasted significantly ($p<0.001$) longer in Group B (466 ± 18.2 minutes) as compared to Group A (334 ± 16 minutes) ($P = 0.000$). It depicted significant prolongation of analgesic effect in the group receiving drugs in a sequential fashion. This difference might be due to the fact that injecting Clonidine and Bupivacaine as a mixture dilutes Clonidine and receptor occupancy might decrease leading to less pronounced effect. And if Clonidine is administered separately a greater spread and therefore formation of stronger bonds with the receptor leading to a denser and prolonged block may occurred. Which was supported by observations of Desai *et al*[8]. Gray *et al*[17] also found that duration of analgesia is increased when IT morphine is administered with normal saline (hypobaric) than with dextrose saline (hyperbaric). Similar to present study observations were made by Jyoti P etall[18] and Thakur A etall[10] also who reported that sequential Clonidine significantly increase the duration of analgesia than when it is given in mixture with hyperbaric Bupivacaine in other surgery like lower limb surgery (Jyoti P etall[18]) and inguinal herniorrhaphy (Thakur A etall[10]).

Present study also found that none Group B cases required analgesic and only 2 cases required vasopressure whereas 3 cases required analgesic and only 3 cases required vasopressure although this difference was not found with significant variation ($P>0.05$) in both the groups. In resonance with these findings Benhamou *et al*[2]. found that when IT Clonidine was administered with HB, none of patients required additional analgesics to obtain an adequate sensory block. So it can be depicted that there is no significant variation ($P>0.05$) in both the groups as per requirement of either analgesic or vasopressure.

It was also observed in the present study that adverse side effects like Hypotension, Bradycardia, nausea and vomiting were also not found with significant variation ($P>0.05$) in both the groups.

So it can be depicted that sequential administration of Clonidine reduces the time to achieve complete sensory and motor block and significantly prolongs the total duration of analgesia without any significant side effects.

CONCLUSIONS

Sequential administration of Clonidine reduces the time to achieve complete sensory and motor block and significantly prolongs along the total duration of analgesia without any significant side effects. Analgesic or vasopressure requirement was almost same whether Clonidine is given in sequential or in mixture with HB. So it can be depicted that sequential administration of Clonidine is better than administering as mixture with hyperbaric Bupivacaine.

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